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# DECREASED ADIPOSE TISSUE ZINC CONTENT IS ASSOCIATED WITH METABOLIC PARAMETERS IN HIGH FAT FED WISTAR RATS

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## ABSTRACT

**Background.** Limited data on adipose tissue zinc content in obesity exist. At the same time, the association between adipose tissue zinc content and metabolic parameters in dietary-induced obesity is poorly studied. Therefore, the primary objective of this study is to assess adipose tissue zinc content and its association with morphometric parameters, adipokine spectrum, proinflammatory cytokines, and apolipoprotein profile in high fat fed Wistar rats.

**Material and methods.** A total of 48 adult female Wistar rats were used in the present study. Rats were fed either control (10% of fat) or high fat diet (31.6% of fat). Adipose tissue zinc content was assessed using inductively coupled plasma mass spectrometry. Rats' serum was examined for adiponectin, leptin, insulin, interleukin-6, and tumor necrosis factor-α using enzyme-linked immunosorbent assay kits. Serum glucose and apolipoprotein spectrum were also evaluated.

**Results.** High fat feeding resulted in a significant 34% decrease in adipose tissue zinc content in comparison to the control values. Fat pad zinc levels were significantly inversely associated with morphometric parameters, circulating leptin, insulin, tumor necrosis factor-α levels and HOMA-IR values. At the same time, a significant correlation with apolipoprotein A1 concentration was observed.

**Conclusion.** Generally, the obtained data indicate that (1) high fat feeding results in decreased adipose tissue zinc content; (2) adipose tissue zinc content is tightly associated with excessive adiposity, inflammation, insulin resistance and potentially atherogenic changes.

**Key words:** zinc, adipose tissue, obesity, endocrine dysfunction, inflammation

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## INTRODUCTION

Zinc is an essential trace element playing a significant role in mammalian biology (Krebs and Hambidge, 2001). Earlier studies have indicated a high importance of zinc in insulin signalling (Jansen et al., 2009). In particular, it activates phosphatidylinositol-3-kinase, protein kinase B and increases insulin receptor β-subunit phosphorylation through suppression of protein tyrosine phosphatases (Vardatsikos et al., 2013). Consequently, it has been considered as one of key trace elements in glucometabolic disorders along with chromium and vanadium (Wiernsperger and Rapin, 2010). Adipose tissue is the functional and morphological substrate of obesity and metabolic syndrome. Adipocyte endocrine dysfunction and adipose tissue inflammation triggers obesity development (Maury and Brichard, 2010). At the same time, it has been supposed that altered adipose tissue trace element profile may aggravate metabolic disruption in obesity (Tinkov et al., 2015a). In particular, we have shown that dietary obesity is associated with impaired adipose tissue chromium and vanadium content in laboratory rodents. Moreover, metal concentration in fat pads is tightly associated with metabolic parameters in animals (Tinkov et al., 2015b). Limited data on adipose tissue zinc content in obesity exist. In particular, it has been shown that high fat feeding results in decreased epididymal adipose tissue zinc content in C57BL/6J mice (Tallman and Taylor, 2003). Similar data were obtained later by Liu et al. (2013). It is also notable, that epididymal but not retroperitoneal and subcutaneous adipose tissue in Diabetic Sand Rat is also characterized by significantly lower zinc content (Maxel et al., 2015). At the same time, the association between adipose tissue zinc content and metabolic parameters in dietary-induced obesity is poorly studied. Therefore, the primary objective of this study is to assess adipose tissue zinc content and its association with morphometric parameters, adipokine spectrum, proinflammatory cytokines, and apolipoprotein profile in high fat fed Wistar rats.

## MATERIAL AND METHODS

A total of 48 female three-months-old Wistar rats were used in the current study. The animal investigation was approved by the institutional Local Ethics Committee. The rats were acclimatized to laboratory conditions for 14 days prior the beginning of the experiment. The temperature in the animal room was 23 ±1°C with 12--hour light cycle.

The animals were divided into two groups ($n$ = 24) with equal initial body weight (Table 1). The rats from group I were fed a control diet, whereas the animals from group II were maintained at a high fat (HF) diet.

A granulated chow ("Orenburg food mixture factory", Orenburg, Russia) containing 270 kcal/100g (20% protein, 70% carbohydrate, 10% fat) was used as a control diet. High fat diet was based on lard supplementation and contained 31.6% of fat from total caloric content. Zinc concentration in the diet types was 30 and 27 mg/kg, respectively. Therefore, the used diets were adequate in zinc (Tallman and Taylor, 2003). The animals had free access to food and drinking water. The total duration of the experiment was 90 days.

Morphometric data were collected at the end of the experiment. In particular, the values of the final weight, total weight gain, body length, body mass index (BMI), abdominal (AC) and thoracic circumference (TC) and their ratio (AC/TC) were calculated. Parametrial and paraovarian adipose tissue (PMAT) was collected through a median laparotomic incision. Based on the values of fat pad weight and body weight adiposity index (AI) was calculated.

The obtained adipose tissue samples were rinsed with ice-cold physiological saline and used for chemical analysis. Zinc content in the obtained fat pads was assessed using inductively coupled plasma mass spectrometry at NexION 300D (PerkinElmer Inc., Shelton, CT 06484, USA) equipped with ESI SC-2 DX4 (Elemental Scientific Inc., Omaha, NE 68122, USA) autosampler. The use of Dynamic Reaction Cell technology during analysis allowed to remove the majority of interferences without the loss of sensitivity.

Rats' serum was examined for circulating insulin (AccuBind), leptin (Biovendor), adiponectin (USCN Life Science Inc.), macrophage chemoattractant protein-1 (MCP-1) (USCN Life Science Inc.), tumor-necrosis factor-α (TNFα) (eBioscience), and interleukin-6 (IL-6) (eBioscience) levels using enzyme-linked immunosorbent assay (ELISA) rat kits at Multiscan Labsystems MS Finland. The obtained values of serum glucose and insulin were used for HOMA-IR calculation.

**Table 1.** Influence of high fat diet on morphometric parameters, apolipoprotein spectrum, insulin resistance parameters, adipokines, and proinflammatory cytokines in Wistar rats

| Parameter | Control diet | High fat diet | *p* value |
|---|---|---|---|
| Initial weight, g | 227.03 ±15.91 | 226.15 ±14.36 | 0.864848 |
| Final weight, g | 297.71 ±19.50 | 310.18 ±34.64 | 0.135280 |
| Weight gain, g | 72.52 ±21.25 | 87.97 ±29.78 | 0.082185 |
| Body length, cm | 21.23 ±0.98 | 20.91 ±0.85 | 0.245265 |
| Body mass index | 0.66 ±0.07 | 0.71 ±0.11 | 0.064851 |
| TC, cm | 15.50 ±0.72 | 15.95 ±0.84 | 0.075443 |
| AC, cm | 17.96 ±0.95 | 18.82 ±1.21 | 0.010145* |
| AC/TC | 1.16 ±0.05 | 1.18 ±0.05 | 0.144582 |
| PMAT, g | 7.61 ±2.28 | 13.13 ±3.45 | <0.000001* |
| Adiposity index, % | 2.54 ±0.68 | 4.21 ±0.86 | <0.000001* |
| ApoB, g/l | 0.030 (0.020–0.030) | 0.020 (0.020–0.030) | 0.432049 |
| $ApoA_1$, g/l | 0.015 (0.010–0.020) | 0.010 (0.010–0.020) | 0.549566 |
| $ApoA_1$/ApoB | 0.50 (0.32–0.85) | 0.50 (0.30–0.50) | 0.569964 |
| Total cholesterol, mmol/l | 1.67 ±0.48 | 1.71 ±0.33 | 0.789859 |
| HDL-C, µmol/l | 1.34 ±0.33 | 1.33 ±0.27 | 0.963642 |
| LDL-C, µmol/l | 0.20 ±0.06 | 0.16 ±0.05 | 0.031613* |
| Triglyceridex, mmol/l | 1.22 ±0.50 | 1.35 ±0.36 | 0.329457 |
| Glucose, mmol/l | 8.89 ±1.16 | 9.49 ±0.78 | 0.046217* |
| Insulin, mIU/l | 3.56 ±0.73 | 3.65 ±0.95 | 0.741896 |
| HOMA-IR | 1.36 ±0.42 | 1.55 ±0.44 | 0.229151 |
| Interleukin-6, pg/ml | 45.25 ±15.44 | 52.75 ±10.44 | 0.171789 |
| Adiponectin, ng/ml | 117.2 (37.5–190.5) | 112.1 (37.7–159.6) | 0.891836 |
| MCP-1, ng/ml | 1.56 (0.27–2.09) | 2.11 (1.1–3.5) | 0.270987 |
| Leptin, ng/ml | 170.6 (135.0–176.8) | 379.0 (310.6–467.4) | 0.000568* |
| TNFα, pg/ml | 0.035 (0.025–0.042) | 0.031 (0.025–0.043) | 0.903353 |

TC – thoracic circumference, AC – abdominal circumference, PMAT – parametrial adipose tissue, ApoB – apolipoprotein B, $ApoA_1$ – apolipoprotein $A_1$, HDL-C – high density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol, HOMA-IR – homeostatic model assessment insulin resistance index, MCP-1 – macrophage chemoattractant protein 1, TNFα – tumor necrosis factor α.
*Significant difference between the groups according to one-way ANOVA or Mann-Whitney U-test.

Serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and glucose were examined with Roche diagnostic kits using "COBAS Integra 400 plus" biochemical analyzer. The concentration of apolipoproteins A1 (ApoA1) and B

(ApoB) was evaluated by immunoturbidimetric method with specific antiserum using "COBAS Integra 400 plus" analyzer.

The obtained data were treated with Statistica 10 (StatSoft Inc., Tulsa, Oklahoma, USA). Data normality was assessed using Shapiro-Wilk test. Normally distributed data were expressed as mean values and the respective standard deviations (mean ±SD). One-way ANOVA and Fisher's Least Significant Difference test was used for group mean comparisons. At the same time, several parameters were not characterized by normal distribution. Therefore, such data were expressed as Median and the respective values of 25 and 75 percentiles (Median(25–75)). Mann-Whitney U-test was used for group comparisons. Correlation analysis was performed using Spearman's correlation coefficient. The significance level for all statistical analyses was set as $p < 0.05$.

## RESULTS

The obtained data (Table 1) indicate that the final weight gain in the HF-fed animals was 21% higher as compared to the control group. No significant changes in body length, thoracic circumference, and BMI were observed. At the same time, high fat-fed rats were characterized by increased AC values. HF feeding resulted in 73 and 66% higher PMAT and AI values in comparison to the control group.

High fat fed animals were characterized by 50% lower serum ApoA1 and ApoB levels as compared to the control group. However, the observed changes were not significant. Despite the absence of changes in serum TC, and HDL-C, dietary intervention significantly altered LDL-C levels. In particular, serum LDL-C concentration in HF-fed animals was 20% lower than in the control ones. TG levels were 11% higher in the adiposity group. However, the observed difference was not statistically significant.

Dietary intervention significantly affected serum glucose levels being 7% higher in high fat fed animals as compared to the control ones. At the same time, no marked alteration of circulating insulin levels and HOMA-IR values was observed. In accordance with morphometric data serum leptin levels were significantly higher in the adiposity group exceeding the control values by more than twofold. However, no expressed changes in circulating levels of adiponectin, MCP-1, IL-6, and TNFα were detected after HF feeding.

Chemical analysis of the sampled fat pads showed a significant 34% decrease in adipose tissue zinc content in high fat fed animals as compared to the control ones (Fig. 1). Correlation analysis (Table 2) was performed to estimate the association between adipose tissue zinc levels and metabolic parameters in rats with excessive adiposity. In the general sample of animals adipose tissue zinc was significantly inversely associated with morphometric parameters like final body weight after dietary intervention, body mass index, and AC/TC ratio. Despite a lack of the influence of diet type on apolipoprotein spectrum, adipose tissue zinc content directly correlated with both apoA1 levels and ApoA1/ApoB ratio values. Metal concentration in the studied fat pad was also inversely associated with insulin levels and HOMA-IR values, as well as with proinflammatory cytokines like TNFα and IL-6. Correlation analysis was also performed separately in the studied animal groups. No significant association between visceral adipose tissue zinc content and morphometric parameters in rats fed a standard diet was observed. At the same time, higher correlation coefficients were revealed for association between AT metal

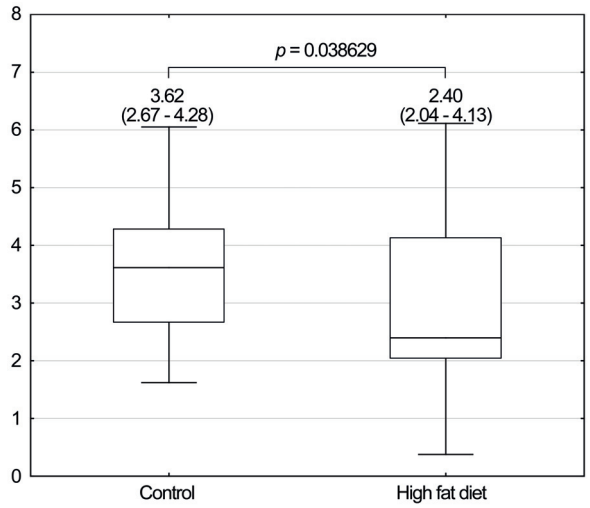


**Fig. 1.** Effect of high fat feeding on adipose tissue zinc content [μg/g] in Wistar rats. Graph represents median (–), interquartile range (□), and non-outlier range (I). *p* value is indicated in accordance with Mann-Whitney U-test

**Table 2.** Correlation between adipose tissue zinc content and the studied parameters

| Parameter | Total sample | Control animals | High fat fed animals |
|---|---|---|---|
| Initial weight, g | –0.100 | –0.140 | –0.083 |
| Final weight, g | –0.314* | –0.186 | –0.445* |
| Weight gain, g | –0.130 | 0.128 | –0.202 |
| Body length, cm | 0.128 | 0.066 | 0.138 |
| Body mass index | 0.029 | 0.228 | –0.062 |
| TC, cm | –0.303* | –0.180 | –0.399 |
| AC, cm | –0.214 | –0.083 | –0.228 |
| AC/TC | –0.370* | –0.363 | –0.299 |
| PMAT, g | –0.287 | –0.127 | –0.239 |
| Adiposity index, % | –0.241 | –0.096 | –0.082 |
| ApoB, g/l | –0.157 | –0.006 | –0.380 |
| $ApoA_1$, g/l | 0.380* | 0.692* | 0.202 |
| $ApoA_1$/ApoB | 0.438* | 0.627* | 0.449 |
| Total cholesterol, mmol/l | 0.074 | 0.010 | 0.147 |
| HDL-C, µmol/l | 0.249 | 0.131 | 0.462 |
| LDL-C, µmol/l | 0.083 | –0.148 | 0.144 |
| Triglyceridex, mmol/l | –0.249 | –0.148 | –0.563* |
| Glucose, mmol/l | 0.091 | 0.261 | 0.099 |
| Insulin, mIU/l | –0.540* | –0.057 | –0.767* |
| HOMA-IR | –0.498* | –0.085 | –0.670* |
| Interleukin-6, pg/ml | –0.164 | –0.343 | 0.143 |
| Adiponectin, ng/ml | –0.213 | –0.433 | 0.442 |
| MCP-1, ng/ml | –0.252 | –0.379 | 0.208 |
| Leptin, ng/ml | –0.662* | –0.667* | –0.729* |
| TNFα, pg/ml | –0.470* | –0.403 | –0.474 |

TC – thoracic circumference, AC – abdominal circumference, PMAT – parametrial adipose tissue, ApoB – apolipoprotein B, $ApoA_1$ – apolipoprotein $A_1$, HDL-C – high density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol, HOMA-IR – homeostatic model assessment insulin resistance index, MCP-1 – macrophage chemoattractant protein 1, TNFα – tumor necrosis factor α.
*Correlation is significant at $p < 0.05$.

levels and serum apoA1 and ApoA1/ApoB values. In the HF-fed group of animals an inverse relationship between adipose tissue Zn and final weight was observed. Moreover, the studied parameter was also inversely associated with serum triglycerides. High fat fed animals were characterized by higher correlation coefficients for the inverse relationship between parametrial zinc content and circulating insulin and

HOMA-IR values. Significant association was also noted between the fat pad zinc content and circulating TNFα both in control and HF-fed animals.

## DISCUSSION

The obtained data confirm earlier indications on the efficiency of high fat feeding in elevating body weight (Buettner et al., 2007). At the same time, we observed a significant increase in parametrial adipose tissue mass that is in agreement with the studies of high-fat feeding induced increase in visceral adipose tissue weight (Lin et al., 2000). Generally, the obtained data indicate that the used model successfully induced excessive adiposity in the laboratory animals. The absence of changes in apolipoprotein spectrum as well as decrease in LDL-C may occur due to the chemical composition of the diet used in the study. In particular, it has been shown that saturated and monounsaturated fatty acids, especially stearic and oleic acids, that are present in lard do not increase serum cholesterol and LDL-C (Grundy and Denke, 1990). The elevation of serum glucose in high fat fed animals indicates a tendency to obesity-associated insulin resistance (Qatanani and Lazar, 2007). Despite the absence of significant changes in serum adiponectin that is frequent in obese state (Haluzik et al., 2004), the experimental animals were characterized by elevated leptin levels being a marker of expanded adipose tissue mass (Maury and Brichard, 2010). Inflammation is one of the mechanisms linking obesity, insulin resistance and other metabolic-related disturbances (Wisse, 2004). At the same time, only slight elevation of proinflammatory cytokines was observed in the obtained animal model being indicative that current dietary intervention did not induce systemic inflammation that is observed in severe obesity (Vendrell et al., 2010).

The obtained data on altered adipose tissue zinc content in HF-fed animals are in agreement with the previously published articles (Liu et al., 2013; Tallman and Taylor, 2003). The inverse association between morphometric parameters of laboratory animals and fat pad metal levels indicate that adipose tissue zinc content is a function of obesity.

The association between elevated serum insulin concentration and HOMA-IR values and the studied metal levels is in agreement with the role of zinc in enhancement of insulin signaling. It has been also demonstrated that zinc potentiates insulin-induced glucose transport in adipocytes (Tang and Shay, 2001).

The inverse correlation between adipose tissue zinc content and circulating leptin levels conforms to earlier indication of increased serum leptin in zinc-deficient state (Lee et al., 2003). At the same time, other work demonstrated reduced leptin production in rat adipocytes in response to zinc deficiency (Ott and Shay, 2001). The inverse association of adipose tissue zinc and circulating TNFα levels supports earlier suppositions on anti-inflammatory role of zinc (Prasad, 2008). In particular, it has been shown that zinc suppresses TNFα production in vitro (Von Bülow et al., 2007). Taking into account overproduction of TNFα in adipose tissue in obesity (Kern et al., 2001), it is supposed that zinc may decrease secretion of this cytokine directly in adipose tissue.

Despite the absence of significant changes in serum apolipoprotein spectrum, adipose tissue zinc level was directly associated with circulating ApoA1 and ApoA1-to-ApoB ratio. Taking into account the association between insulin resistance and alteration of apolipoprotein A1 metabolism (Pont et al., 2002), it is supposed that adipose tissue zinc content may be associated with ApoA1 levels through modulation of insulin resistance.

It is also notable that the observed associations were significant despite the absence of marked differences between the group values. Consequently, adipose tissue zinc may be potentially used as an early biomarker of metabolic disruption in obesity. However, additional studies are required to highlight the mechanisms of such association.

Generally, the obtained data indicate that (1) high fat feeding results in decreased adipose tissue zinc content; (2) adipose tissue zinc content is tightly associated with excessive adiposity, inflammation, insulin resistance and potentially atherogenic changes.

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